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What is a vertebrate pigment cell?

by

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Abstract

On the basis of discussions emerging from a workshop and discussions at the 7th meeting of the European Society for Pigment Cell Research in Geneva in 2012 this manuscript outlines useful criteria for defining the bona-fide pigment cells as a functional entity of the vertebrate body plan and differentiating them from “pigmented” cells in general. It also proposes a nomenclature for the various types of pigment cells of vertebrates.

Pigment cells and their pathological derivatives are the focus of a large and active research community whose work impacts on many areas of biology and medicine. However, if one looks for a definition of what constitutes a pigment cell, one has to go back to the sixties of the last century. As a result of the Sixth International Pigment Cell Conference, held in 1965 in Sofia, Bulgaria, a nomenclature committee, headed by Thomas Fitzpatrick and Walter Quevedo, put forward a definition (Levine et al., 1966) that reflected the actual knowledge at this time. It centred around the presence of melanosomes within the cytoplasm. Melanosomes were defined and classified in the early 1960s by Seiji and colleagues (Seiji et al., 1961). The nomenclature included melanocytes, melanoblasts, the pigment dispersing melanophores of poikilothermal vertebrates, and the Langerhans cells. Cells containing other types of pigment were not considered.

Since then our knowledge has increased enormously. Thanks to the advent of molecular biology in pigment cell biology, the outstanding analytical power of modern imaging techniques and the functional insights from animal model studies we now have a much better understanding of the structure and physiology of normal and malignant pigment cells. The remarkable progress in the field should be motivation enough to put forward an updated definition and terminology for pigment cells that might guide the research community to ensure that we all mean the same thing when we use certain terms and that a lot of the inconsistencies and confusion in the current and past literature can be clarified. As all attempts to make definitions and nomenclature suggestions naturally can only reflect the personal view and knowledge of the authors, we hope that this paper will evoke lively discussion in the community and, where appropriate, further research, to improve the criteria and descriptions given below.

Definition of “Pigment Cell”

Ideally, such a definition should be applicable to all animals, but given that our knowledge about pigmentation in invertebrates remains far less complete than in chordates (and even for those, data are only collected for a handful of species), we will restrict the following considerations to the latter group. We propose the following definition:

*“A pigment cell is a **primarily pigmented cell** that **actively generates membrane-bound organelles to impart color** by containing chromophoric substances or structures, as well as the lineage specific non-pigmented precursors specified to develop into such a pigmented cell, and the pathological derivatives of pigment cell lineages”* (Table 1).

By ‘primarily pigmented’, we mean that the cell synthesises or assembles the pigment, rather than being pigmented due to transfer of pigmented organelles from another cell (secondary pigmentation). Pigment cells as so defined will often have one of two primary functions, in absorbing stray light to enhance the acuity of a visual apparatus, or in providing pigmentation visible to other organisms. However, in many cases the extant function of pigmented cells will often be unknown (e.g. pigmented cells of internal organs), and in some cases (e.g. melanocytes in the stria vascularis) may not involve their pigmentation *per se*. Nevertheless, where their developmental (and evolutionary) origin is shared with that of integumentary pigment cells, in which coloration is (or is likely to be) the functionally important feature, they should clearly be classified the same way. Indeed, we suggest that in vertebrates the common developmental origin, where known, provides a useful supporting criterion, since wherever developmental origin has been explored, all pigment cells are descendants of the neuroectoderm and derive either from the neural crest or the optic cup (Dutton et al., 2001; Kelsh and Barsh, 2011; Parichy and Spiewak, 2015; Rogers et al., 2012; Silver et al., 2006; Thomas and Erickson, 2008).

Another developmental biological aspect appears useful to explain what singles out the pigment cells from all the pigmented cells, namely that it executes a genetically encoded differentiation programme to produce pigmented subcellular components that impart colour.

We include in our definition that the pigment be in membrane-bound organelles because it is currently the case that all cells whose primary function is the generation of color do so through an organelle-based mechanism. Furthermore, these organelles represent an essential specialisation ensuring appropriate conditions for rapid pigment synthesis (e.g.

melanin) or assembly (e.g. guanine crystals) can be achieved without compromising the cell.

We consider it is important that the pigments impart coloration to the cell, but we note that many vertebrates can detect UV wavelengths and would emphasise that pigments that are detectable at such wavelengths, even if not visible to humans, should be included, so long as they do, or ancestrally were likely to, result in colouration that is functionally significant. However, based on the definition proposed, it is clear that not every cell containing pigments would be considered a *bona fide* pigment cell. Thus, we exclude the following cell-types, for the reasons given:

- (i) cells, like keratinocytes, that are secondarily pigmented through the uptake of pigment-containing organelles from *bona fide* pigment cells, as well as the various macrophage lineages that contain melanin from phagocytosed pigment cells
- (ii) erythrocytes, because their pigment is not contained within membrane-bound organelles
- (iii) dopaminergic neurons containing neuromelanin, because the slow, progressive accumulation of this pigment in these cells is most consistent with it being a waste product or having another role rather than having a function in colouration (Mann and Yates, 1974).
- (iv) cells containing lipofuscin, since this pigment appears as an aging-related product in cell types and is not imparting colour as part of the physiological function of this cell type
- (v) muscle cells in some fish (e.g. salmon) which exceptionally may appear red because of carotenoids
- (vi) photoreceptor cells, in which the pigment does not generate visible coloration

Our definition needs to be broad to encompass all the known pigment cell-types and to allow the incorporation of the new pigment cell-types likely to be discovered in the future. Our knowledge of pigment cells in the very diverse and more basal vertebrate groups, especially teleosts, is still far from complete, and it is likely that the current list of distinct cell-types is incomplete.

Nomenclature of pigment cells

Pigment cells, as so defined, are also known by the generic term “chromatophores” in vertebrates other than mammals and birds. Our definition of pigment cells immediately proposes a scheme for their classification, and a unifying terminology (Figure 1). The major separation is made primarily on the type of pigment they contain, namely those that synthesise melanins (including pheomelanin) and those containing non-melanin pigments, and secondarily on their embryonic origin.

Melanocytes

Classically, melanocytes represent the final differentiation stage of a cell lineage derived from the neural crest. They are found in all vertebrates and are generally the most widespread type of pigment cells. They are characterized by the presence of either black eumelanin or yellowish pheomelanin or both, although in some lineages, such as fish, pheomelanin has not so far been found (d'Ischia et al., 2015; Kottler et al., 2015). A second source of eumelanin-containing pigment cells is the optic neuroepithelium, which gives rise to the retinal pigment epithelium, a single cell layer abutting the photoreceptor layer in the vertebrate eye. By our definition, retinal pigment epithelium cells are also “melanocytes” despite their different embryological origin. In general, both neural crest-derived and optic neuroepithelium-derived melanin-containing pigment cells are determined by the transcription factor MITF even though there are species-specific exceptions. For instance, in zebrafish, *Mitf* is not necessary for RPE development (Lane and Lister, 2012).

In melanocytes, melanin is contained within membrane-bound organelles called melanosomes. Neural crest-derived melanocytes can be further classified according to whether they actively transfer melanosomes to other cells - the melanin-transferring melanocytes – or not. The melanin-transferring melanocytes are those typically found in the epidermis of mammalian and avian skin, which secrete melanosomes that then are taken up by neighbouring keratinocytes, to impart coloration to the skin and to hair and feathers. Non-transferring melanocytes are found in the dermis and non-cutaneous locations in mammals, avians, reptiles, amphibians and fish.

Melanin transfer also occurs as a special feature of mammalian melanocytes as part of the adaptive response to sunlight. Lower vertebrates have an even more elaborate means to perform “colour change”, but this is based on different cell biological mechanism(s). Here

melanosomes are either actively dispersed throughout the cytoplasm (associated with a centrifugal movement of the melanosomes) or concentrated perinuclearly (associated with a centripetal movement of the melanosomes), giving the melanocyte either a more expanded or reduced light absorbing appearance. The melanosome-dispersing ability of a subpopulation of melanocytes of teleosts, amphibians and reptiles, contrasting as it does with the melanin transfer of many mammalian melanocytes, so intrigued pigment cell researchers that they reserved a specific name, melanophore, for this melanocyte. Introducing this additional category had the advantage of providing more precise classification of cell behaviour, but was not consistent, as other subtypes e.g. the melanin-secreting melanocytes of mammals, were not treated similarly. For the sake of simplification of the nomenclature and in recognition of the increasing evidence for the conserved genetics of melanocyte biology, we propose that all these cells may simply be referred to as melanocytes.

We are aware that elimination of the historical term “melanophore” may create some confusion. Thus, we propose that, where they feel it appropriate, authors may explain this terminology adjustment to their readers.

Pigment cells without melanin

Pigment cells that contain biomolecules other than melanin that either reflect or adsorb light are typically found in the poikilothermic vertebrates. Several types have been documented as being retained in the iris of birds, although molecular characterisation has yet to be performed to evaluate the homology of these cells to those in poikilothermic vertebrates (McGraw and Nogare, 2004; Oliphant, 1981). In proposing the following classification, we build on the synthesis of Bagnara and Matsumoto (Bagnara and Matsumoto, 2006). We classify the non-melanin-containing chromatophores initially by primary mode of colouration (reflective or light absorbing), and then by colour. The relationship of these properties to the pigments contained is only partially worked out, and it should be noted that two or more classes of pigments are often found in different cell-types (see also below: “Atypical pigment cells”), in part explaining the range of colours each may show.

We distinguish two types of reflecting pigment cells, iridophores (iridescent or white, reflective) and leucophores (white) (Oliphant and Hudon, 1993). Iridophores and

leucophores can be distinguished by the structure of their organelles (reflecting platelets or leucosomes). Iridophores contain thin, plate-like (flattened) reflecting platelets composed of purine crystals and look iridescent when arrangements of the platelets are precisely organised or look white when they are less organised. Leucophores typically also contain the purine compound uric acid, but this is contained within smaller and more rounded organelles termed leucosomes. Generally, these two cell-types can also be distinguished by their cell shapes and/or by their ability to aggregate and disperse their reflective organelles: iridophores are rather round in shape and typically lack the ability to aggregate and disperse their reflecting platelets (but see below), whereas leucophores are dendritic like other cell types (melanocytes, xanthophores, erythrophores and cyanophores) and their leucosomes can aggregate and disperse. The aggregating-dispersing responses of leucophores occur in directions opposite to those of light-absorbing pigment cells. When melanosomes move centripetally, for instance, in response to noradrenaline, leucosomes move centrifugally. A dendritic iridophore in the dermis of the freshwater goby (*Odontobutis obscura*) shows a unique physiological trait in that the reflective organelles show the morphology of reflecting platelets, but are unusual in that they are motile (Matsuno and Iga, 1989). We would suggest that their classification as iridophores is retained on the basis of the morphology of the organelles.

Among light absorbing, non-melanin pigment cells we distinguish xanthophores and erythrophores (yellow and red respectively, due to pterinosomes and/or carotenoid vesicles), and cyanophores (intense blue, due to cyanosomes containing an unknown blue pigment) (Table 1). The varied content of pteridines and carotenoids determines the range of yellow to red colouration in xanthophores and erythrophores; no molecular or structural markers specific to either xanthophore or erythrophore have been identified. Thus the distinction of these two cell types is currently not well defined and may be semantic.

Other cell-types no doubt remain to be identified; one prime location to look might be the feather follicles of parrots, within which are likely to be found cells synthesising and secreting the psittacofulvins which give this group their striking red, orange and yellow plumage colours (McGraw and Nogare, 2004). Similarly, red fluorescent chromatophores have been identified in tropical reef fish, including from the eye ring of tropical goby species and the black-faced blenny (*Tripterygion delaisi*), and in dendritic

chromatophores in the integument of Gold Neon Eviota Goby (*Eviota pellucida*) (Michiels et al., 2008; Wucherer and Michiels, 2014; Wucherer and Michiels, 2012). Their combination of red colouration with reflecting platelets in a dendritic cell suggests that they might be an unusual type of iridophore, but further characterisation of their organelles might confirm they form a novel cell-type.

In general chromatophores are likely to derive from the neural crest, although a reflecting cell layer, which we would classify as consisting of leucophores, in the retinal epithelium in birds seems most likely to be derived from the RPE (Hudon and Oliphant, 1995). For cyanophores so far their embryological origin has not been documented but their ultrastructural organisation, shape and location in the integument makes it reasonable to assume a similar lineage relationship as for the other pigment cell types of the fish skin. However, given Nature's ability to surprise, we feel it would be unwise to rule out the possible origin of novel pigment cell types (*sensu stricto*) from other tissues, so that testing of the robustness of this supporting criterion will be an intriguing aspect to studies of novel pigment cell-types discovered in the future.

Non-melanin pigment cells are present at cutaneous and non-cutaneous sites and subpopulations exist that are involved in colour change. The latter depends upon cytoskeleton-dependent movement of pigment-containing organelles within the cytoplasm. Again, it is proposed not to use further sub classification into “-cytes” and “-phores”, in particular as the terms leucocytes or erythrocytes are already used for non-pigment cells. Thus, for clarity and consistent with historical use, we propose the continued use of the suffix “-phore” for all non-melanin pigment cells.

Polychromatic pigment cells

Pigment cells that cannot be encompassed by the above classification have been identified in some poikilothermic vertebrates. Dichromatic chromatophores, having two types of distinguishable pigment compounds or organelles have been reported. Recently, erythro-iridophores, which possess light-reflecting platelets and reddish carotenoid pigments, were found in *Pseudochromis diadema* (Goda et al., 2011), and light absorbing polychromatic chromatophores, which contain cyanosomes, pterinosomes and carotinoid vesicles in their cytoplasm, have been found in the integument around the margins of the bluish regions of the mandarin fish (*Synchiropus splendidus*) (Goda et al., 2013). We

propose the name erythro-cyanophore for the latter. In the case of erythro-iridophores, it is unclear where the carotenoids are accumulated (most likely cytoplasmic, or perhaps in reflecting platelets?). It would certainly be interesting to assess the developmental origin of erythro-iridophores, to establish whether they are modified iridophores that have co-opted the ability to accumulate carotenoids.

Interestingly, leucophores can also contain pteridines (drosopterine) and thus look orange during embryonic/larval stages in medaka (H.H., unpub. obs.). The developmental genetics of leucophores and xanthophores in medaka has suggested that development of these cell-types shares a common cell lineage different from that of melanophores and iridophores, so that developmentally leucophores are more closely-related to xanthophores than to iridophores (Kimura et al., 2014; Nagao et al., 2014; Oliphant and Hudon, 1993). Nevertheless, given the common presence of multiple pigmented organelles and the frequent ignorance regarding their chemical components, we prefer to maintain the tradition of classifying by mode of colouration and colour. This means that we would also classify so-called ‘reflecting xanthophores’ in the bird iris, which are shiny yellow due to crystalline pteridines (or mixtures of pteridines and purines) within reflecting platelets (Oliphant and Hudon, 1993), as iridophores.

Non-pigmented precursor cells

In their derivation from the neural tube or from neural crest cells, all pigment cells transition through non-pigmented stages to their fully-pigmented, fully differentiated state. We distinguish any cell that shows evidence of fate specification to a pigment cell fate using the generic term chromatoblast, and distinguish melanoblasts, iridoblasts, leucoblasts, erythro-iridoblasts, xanthoblasts, erythroblasts and cyanoblasts, as appropriate (Table 1). We have taken the pragmatic decision to refer to fate specification, and not commitment, since, in reality, it is essentially impossible to evaluate commitment *in vivo*, and rarely testable *in vitro*. In contrast, a ‘specified’ cell is readily defined as one showing specific molecular, cellular or behavioural features characteristic of a specific pigment cell lineage, and we explicitly recognise that this does not require that the cell is determined i.e. committed to that lineage. We think it is important to include specified precursors within the definition, for the same reason that we consider an albino melanocyte to still be a melanocyte i.e. it expresses a recognisable pattern of melanocyte-specific genes, regardless of whether melanin is synthesised in detectable amounts or not.

Neoplasms of pigment cells

When pigment cells undergo neoplastic transformation, these pathological derivatives are usually termed according to the pigment that characterized the original cell lineage: melanoma cells from melanocytes, erythrophoroma cells from erythrophores, xanthophoroma cells from xanthophores, etc. Those tumors in poikilothermal vertebrates, which contain more than one cell type, are classified as chromatophoromas. Pigment cell tumors are very heterogeneous with respect to many cellular features; this includes degree of pigmentation (sometimes complete absence of pigment), shape, capacity to proliferate and/or to migrate. The morphological variation in pigment cell neoplasms that occur in different species is also extensive and complicates comparative evolutionary studies.

With respect to the cell types that deviate from the normal, physiological differentiation path, the nomenclature committee that identified the 1966 nomenclature for the normal pigment cells also proposed a classification for the pathological series, but this is not in use any more. An extensive literature exists for the classification of human melanocytic neoplasia (Eduardo Calonje et al., 2011). A variety of benign melanocytic neoplasms are recognized and include common nevi, dysplastic nevi, blue nevi, cellular blue nevi, deep penetrating nevi, and Spitz nevi. Melanocytic nevi are clonal proliferations of melanocytes that retain many of the cytological features of melanocytes, but have altered growth patterns, frequently forming nests or clusters. In contrast cutaneous melanocytes typically maintain a net-like pattern at the epidermal/dermal junction and rarely are directly adjacent to other melanocytes. Melanoma variants comprise the vast majority of malignant pigment cell neoplasms. Melanoma can arise spontaneously in a variety of animals, including dogs, horses, pigs and several fish. Melanoma can also be induced by exposure to UV irradiation, following exposure to carcinogens, or by the presence of relevant genetic changes in melanocytes. Similar genetic changes in other species can result in analogous melanocytic neoplasia. One example is the observation that Gnaq and Gna11 mutations both result in similar blue nevus-like dermal melanocytic proliferations in mice and humans (Bastian, 2014). In recent years, a variety of genetic changes have been characterized in human melanocytic neoplasms and often correlate strongly with specific morphological characteristics (Bastian, 2014). About half of all melanoma in

humans harbour oncogenic mutations in the BRAF gene. Mutations in NRAS, CDKN2A, NF1, p53, and PTEN also play a role in melanoma formation (Bastian, 2014). While progress has been made on defining the genetic changes present in melanoma, much remains to be learned about the specific characteristics of malignant transformation of the distinct pigment cell populations discussed above.

Molecular markers of pigment cells

On current knowledge, molecular markers distinguishing pigment cell-types can only be tentatively assigned, because whilst melanocytes have been extensively studied, knowledge of other cell-types lags behind. We propose here some putative markers (Table 1), but note that further exploration of the genetics and molecular biology of diverse pigment cells will be necessary before any of these can be considered confirmed. One common feature of melanocytes is their genetic dependence on the transcription factor Mitf (Lister, 2002; Steingrimsdottir et al., 2004). Identification of key factors driving fate specification and differentiation of other cell-types will be invaluable, but this will be non-trivial for those cell-types found only in non-model organisms, e.g. cyanophores. In many respects, biosynthetic enzymes involved in pigment synthesis are useful markers, but this is complicated by the presence of multiple pigment types in some pigment cells (e.g. leucophores). In practice, this means that, depending on the cell-type, two or more markers may be required to definitively identify pigment cell types.

Further progress in pigment cell research will certainly not only increase our understanding of pigment cell biology but also give the opportunity to improve and perfect the definition of what a pigment cell is.

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Figure and table legends

Table 1: Pigments and pigment cell types

Figure 1: Classification of vertebrate pigment cells

1 (Keratinocytes, Melanophages and Kupffer cells)

2 Xanthophores (yellow) Pteridine, Carotenoid (passive), Erythophores (red): Pteridine, Carotenoid (passive), Leucophores (white): Pteridine, Uric acid, Iridophores (iridescent color) (+Visceral): Purine-crystalized platelet, Cyanophores (blue): ?

3 Transferring Mc: Epidermal melanocytes (interfollicular + follicular)

Pigment cell	Precursor	Pigment	Pigment-containing organelle	Pigment cell derived tumor	Putative molecular markers	Distribution ¹
Absorptive						
Melanocyte	Melanoblast	Melanin, Pheomelanin	Melanosome	Melanoma	Mitf, Dct, Tyrosinase	All vertebrates
Xanthophore	Xanthoblast	Pteridines, carotenoids	Pterinosome, carotenoid granule	Xanthophoroma	Xdh, Gch	Avians, reptiles, amphibians, fish
Erythrophore	Erythroblast	Pteridines, carotenoids	Pterinosome, carotenoid granule	Erythrophoroma	Xdh, Gch?	Reptiles, amphibians, fish
Cyanophore	Cyanoblast	Unknown	Cyanosome	Cyanophoroma ²	Unknown	Fish
Reflective						
Iridophore	Iridoblast	Crystalline purines or pteridines	Reflecting platelet	Iridophoroma	Ltk, Pnp4a	Avians, reptiles, amphibians, fish
Leucophore	Leucoblast	Crystalline purines, pteridines	Leucosome (Pterinosome, others ³)	Leucophoroma	Xdh, Gch in embryonic leucophores	Avians? reptiles, amphibians, fish
Dichromatic						
Erythro-iridophore	Erythro-iridoblast	Crystalline purines, carotenoids?	Reflecting platelet (others?) ⁴	Erythro-iridophoroma ²	Unknown	Fish
Erythro-cyanophore	Erythro-cyanoblast	Pteridines, carotenoids, unknown	Pterinosome, carotenoid granule, Cyanosome	Erythrocyanophoroma ²	Unknown	Fish

¹ Note that distribution of non-melanocyte cell-types is only poorly explored in birds and requires further investigation in the case of mammals

² not reported so far

³ not known if pteridines are contained in the leucosome or in separate organelles

⁴ location of carotenoids currently unclear, maybe cytoplasmic?

Table 1: Summary of key pigment cell-types and distinguishing characteristics

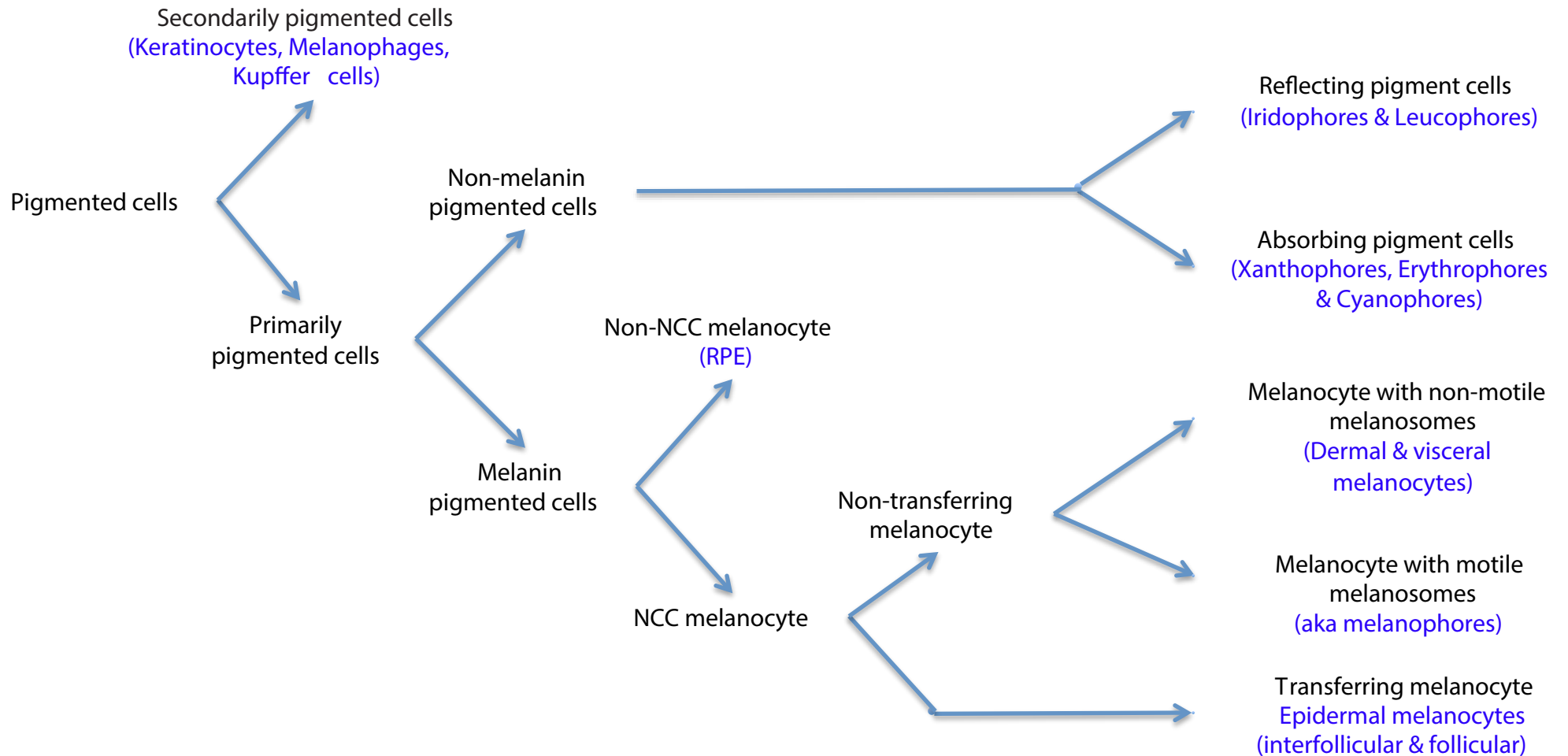


Figure 1

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